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REVIEW

Botulinum toxin A in idiopathic overactive bladder: a narrative review of 5410 cases

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Introduction: *When conservative treatments fail, botulinum toxin A (BoNT-A) is an option for refractory idiopathic overactive bladder (OAB). This review evaluates the efficacy, safety, and predictive factors for BoNT-A in this situation.*

Material and Methods: *A literature search up to January 2025 was performed using PubMed, Google Scholar, and Embase to assess efficacy, safety, and predictors of adverse events (AE) related to BoNT-A. The risk of bias was assessed using the Risk of Bias 2 (RoB 2) tool for randomized studies and the Critical Appraisal Skills Programme (CASP) checklist for cohort studies. The quality of the review was evaluated based on the Oxford criteria, following the Strengthening the Assessment of Narrative Review Articles (SANRA) guidelines, and by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.*

Results: *31 studies were included, involving 5410 patients. BoNT-A improves OAB symptoms even after reinjections. Higher doses do not enhance efficacy but increase AE. AE includes high post-void residual (PVR), clean intermittent self-catheterization (CISC), and Urinary Tract Infection (UTI). Predictors of CISC include age, male gender, hysterectomy, ≥3 vaginal deliveries, mixed incontinence, prior mid-urethral sling (MUS), high PVR, low Pressure at Pdet at First Micturition (PIP1) in women, low Bladder Compliance Index (BCI) in men, and high Bladder Outlet Obstruction Index (BOOI). Diabetes and heart failure increase PVR. UTIs are more frequent in women and men with benign prostatic hyperplasia, with CISC increasing the risk fivefold. Severe complications are rare. Predictors of poor response include male gender, high BOOI, low urinary flow, and diabetes.*

Discussion: *BoNT-A is effective for OAB, especially for incontinence. AE is dose-dependent and limits treatment adherence. Their link with poor response remains unclear.*

Conclusion: *BoNT-A effectively treats refractory idiopathic OAB, improving symptoms and quality of life with repeated injections.*

Key Words: botulinum toxin A, idiopathic OAB, urodynamic parameters, adverse effects, efficacy criteria, predictive factors

Introduction

Overactive bladder (OAB), defined by the International Continence Society (ICS), is characterized by urgency, with or without urinary incontinence (UI), frequent urination, or nocturia, without apparent pathology.[1] The predominant cause is detrusor overactivity (DO), diagnosed urodynamically as involuntary detrusor contractions during bladder filling. DO manifests as neurogenic (associated with neurological conditions) and non-neurogenic (often termed idiopathic). Prevalent, overactive bladder (OAB) affects up to 16% of young adults, impacting quality of life and healthcare costs, with recognized risk factors including age, gender, menopause, and obesity.[2]

Primary OAB treatment includes pharmaceutical options like anticholinergics and beta-3 adrenergic receptor agonists when behavioral therapies

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fail. Anticholinergics, the gold standard, have high discontinuation rates due to side effects.[3] When conservative therapies prove ineffective, minimally invasive treatments like posterior tibial nerve stimulation, sacral neuromodulation, and intradetrusor injections of botulinum toxin A (BoNT-A) can be considered. In 2013, BoNT-A received validation from the Food and Drug Administration[4] for refractory idiopathic OAB management.

The existing literature on BoNT-A for refractory idiopathic OAB is highly heterogeneous,[5] with inconsistent definitions of efficacy, poor response, and varied outcome measures.[6] There is no standardized approach to assessing patient-reported outcomes (PROs) or quality of life,[7] and follow-up intervals differ widely across studies,[8] limiting the ability to compare results. These gaps hinder clear conclusions about the treatment's effectiveness and risks.

This review provides an overview of the field, focusing on the efficacy, safety, and factors that may predict poor response and adverse events following BoNT-A treatment for refractory idiopathic OAB.

Materials & Methods

Search strategy

This analysis was conducted by the principles outlined in the Scale for the Assessment of Narrative Review Articles (SANRA) and the guideline recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A prospective protocol was developed before initiating this review to ensure a structured and systematic approach.

A comprehensive search was performed up to January 2025, using PubMed, Google Scholar, and Embase databases. No restrictions were applied regarding language or publication date. The research question was framed using the PICO methodology:

- P (Population): Adult patients with idiopathic OAB
- I (Intervention): BoNT-A
- C (Comparison): Placebo or other treatments (e.g., anticholinergics)
- O (Outcome): Improvement in symptoms of OAB, including voiding frequency, urgency, incontinence episodes, nocturia, and quality of life

To address this, Medical Subject Heading (MeSH) terms and relevant keywords were used individually to ensure a thorough search. The specific search terms included: "*Botox*" OR "*botulinum toxin A*", "*OAB*" OR "*idiopathic overactive bladder*" OR "*overactive bladder*", "*effectiveness*" OR "*efficacy*", "*side effect*" OR "*adverse effect*", "*predictors*", "*outcome*".

References from relevant studies were also manually screened to identify additional pertinent research. Once potential studies were identified, duplicate entries were removed, and the articles underwent an additional screening process to ensure they met the predefined criteria. Figure 1 shows the study selection flow chart based on PRISMA guidelines.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Adults aged 18 years or older. (2) Patients with idiopathic overactive bladder. (3) Treatment with intradetrusor injections of BoNT-A, regardless of the dose. (4) Randomized controlled trials (RCTs), cohort studies, or case-control studies. (5) Comparisons including (a) Efficacy or AE of different doses of BoNT-A compared to placebo or (b) responses to BoNT-A, with a focus on either good and poor responders or comparisons between patients reporting AE and those who did not.

The exclusion criteria included: (1) Children. (2) Neurogenic overactive bladder. (3) Use of botulinum toxin other than type A. (4) Non-comparative studies, reviews, commentaries, conference abstracts, editorials, practice surveys, guidelines, and case reports.

Outcome measures

The following outcome measures were assessed: efficacy of BoNT-A (symptom improvement and urodynamic criteria), adverse events AE (tolerance, need for self-catheterization, elevated post-void residual volume (PVR), and urinary tract infections (UTI)), poor response to BoNT-A, and predictive factors for AE.

Study selection and data extraction

The study selection process consisted of two phases. The first phase involved screening titles and abstracts to identify potentially relevant studies. In the second phase, a full-text review was conducted for selected articles. Two independent reviewers assessed eligibility based on predefined criteria, with any disagreements resolved through discussion or consultation with a third reviewer.

The data extracted included: study description (first author, year, type of study, sample size, toxin dose, injection method, inclusion criteria, and follow-up), efficacy outcome criteria, average variation in parameters (such as frequency, urinary incontinence, and urodynamics), AE, and their predictive factors.

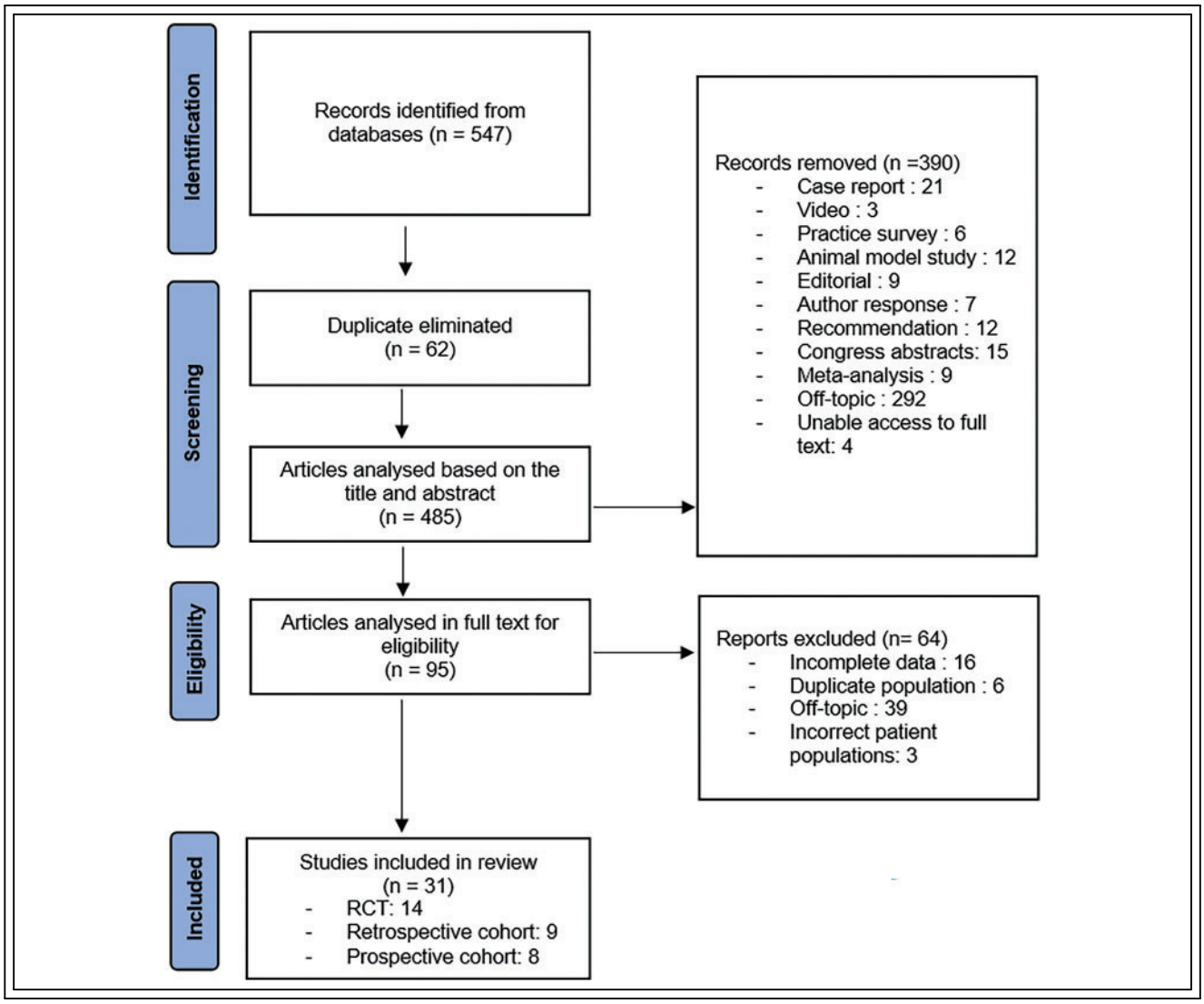

FIGURE 1. Study selection flow chart

Quality assessment

We assessed the quality of the studies using the Oxford criteria (OCEBM Levels of Evidence).

Biais analysis

We used bias analysis using the Risk of Bias 2 (RoB 2) tool for randomized studies and the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (Tables 1 and 2).

Data analysis

The extracted data were analyzed and presented in tabular and graphical formats. Descriptive statistics were employed for quantitative analysis. A comprehensive narrative synthesis was conducted to systematically summarize the findings from the included studies.

Results

Characteristics of included studies

The initial search identified 547 articles across three databases. After removing 62 duplicates, 485 studies underwent title/abstract screening, resulting in the exclusion of 386 records. Four additional articles were excluded due to unavailability of full texts. Following full-text assessment of the remaining 95 articles, 64 studies were excluded based on eligibility criteria (Figure 1).

TABLE 1. **Risk of bias in randomized controlled trials assessed using the ROB 2 tool**

Reference	Bias from randomization	Bias from intervention deviations	Bias from missing outcome data	Bias from outcome measurement	Bias from reporting selection
Brubaker et al., 2008[9]	Low	Some concerns	Low	Low	Low
Sahai et al., 2008[10]	Low	High	Some concerns	Low	Some concerns
Flynn et al., 2009[11]	Low	Some concerns	Low	Low	Low
Cohen et al., 2009[12]	Low	Some concerns	Low	Low	Low
Dmochowski et al., 2010[13]	Low	Low	Low	Low	Low
Altaweel et al., 2011[14]	Low	Some concerns	Some concerns	Low	Low
Dowson et al., 2011[15]	Low	Some concerns	Some concerns	Low	Low
Rovner et al., 2011[16]	Low	Low	Low	Low	Low
Denys et al., 2012[17]	Low	Low	Low	Low	Low
Fowler et al., 2012[18]	Low	Low	Low	Low	Low
Tincello et al., 2012[19]	Low	Some concerns	Low	Low	Low
Nitti et al., 2013[20]	Low	Low	Low	Low	Low
Chapple et al., 2013[21]	Low	Low	Some concerns	Low	Low
Yokoyama et al., 2020[22]	Low	Low	Low	Low	Low

The final analysis included 31 studies: 14 randomized controlled trials (RCTs), 9 retrospective cohort studies (RCs), and 8 prospective non-randomized cohort studies (PCs), encompassing a total of 5410 patients. All studies were published in English between 2006 and 2025. The characteristics of the included studies are presented in Table 3.

Efficacy

Variability in outcome measures

The 31 included studies evaluate the efficacy of BoNT-A injections. 25 studies use different scores to assess symptom improvement. This variability poses challenges. Urgency, a key symptom of OAB, remains difficult to assess objectively due to its subjective nature and patient variability. Patient expectations also influence treatment perceptions, with partial symptom relief sometimes perceived as failure if complete resolution was expected. 6 studies utilize urodynamic parameters to provide objective measurements. However, these assessments are invasive, poorly tolerated, and impractical for long-term monitoring due to BoNT-A's temporary effects. This variability in assessment criteria introduces potential bias. Table 4 highlights these differences in outcome measures.

Efficacy on symptoms

All studies demonstrate greater efficacy of BoNT-A at 3 months compared to placebo. Regarding voiding frequency, 16 studies report an average reduction of −2.55 micturitions per 24 h with BoNT-A across all doses, compared to −0.73 with placebo, with a maximum reduction of over –5 micturitions in 3 studies (Figure 2). For urinary incontinence (UI), 16 studies, show a reduction of −2.57 episodes per 24 h with BoNT-A, compared to 0.64 with placebo, with a maximum reduction of −4.5 episodes in Flynn[11] and Tincello's[19] studies. Up to 25% of patients achieve complete continence (Figure 3). Additionally, BoNT-A improves nocturia, patient satisfaction, and overall quality of life.[21] The effects of BoNT-A appear quickly, with urgency episodes typically reduced by the 8th day and peaking between the 2nd and 8th week.[23,29] Long-term follow-up in Nitti[20] and Chapple's[21] studies found an average efficacy duration of approximately 24 weeks with a 100U BoNT-A dose.

Urodynamic changes post injection

9 studies assess changes in urodynamic parameters post-injection, with mixed results. Only 4 studies[10,16,17,30] report a significant decrease in maximum detrusor pressure (P_{det} max), averaging −10 cmH_2O, although not for all doses. All studies show an increase in maximum cystometric capacity (MCC), ranging from +71 to +138 mL, though not consistently across all doses. The results for Volume at the first detrusor contraction (VFDC) vary: 3 studies[10,16,32] report significant improvements (+23.1 to +59 mL), 2 show no significant change,[14,15] and 2 find improvement only at higher doses (above 150U).[10,16]

TABLE 2. **Risk of bias in cohort studies assessed using the CASP**

Reference	Clear research question?	Participants randomized concealed?	Similar baseline?	Blinded staff?	Follow-up?	Intention-to-treat?	Same care in groups?	All effects reported?	Bias addressed?	Benefits outweigh risks and costs?	Results locally applicable?	Results consistent with other studies?
Schmid et al., 2006[23]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	P (M.L)	Y	Y
Sahai et al., 2009[24]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Kuo et al., 2010[25]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Liao et al., 2013[26]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Wang et al., 2014[27]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Osborn et al., 2015[28]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Hsiao et al., 2016[29]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Owen et al., 2017[30]	Y	N	P	N	Y	Y	Y	Y	P (M.L)	Y	Y	Y
Miotla et al., 2017[31]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Richter et al., 2017[32]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Kennelly et al., 2018[33]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Liberman et al., 2018[34]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Faure Walker et al., 2019[35]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Abrar et al., 2020[36]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Mateu Arrom et al., 2020[37]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
El Issaoui et al., 2024[38]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y
Nurkkala et al., 2025[39]	Y	N	P	N	Y	Y	Y	Y	P (attrition)	Y	Y	Y

Note: Y = Yes; N = No; P = Partial; Attrition bias = Bias due to incomplete outcome data (i.e., loss to follow-up); M.L = Moderate losses = Moderate number of participants lost to follow-up, not sufficient to invalidate results but potentially impacting robustness.

TABLE 3. **Characteristics of the included studies**

Authors	Year	Type	Patient (n)	Dose (U)	Injection method	Inclusion criteria	Follow-up (mo)	LE
Schmid et al.[23]	2006	PC	100	100	30 ID Sparing trigone	☐ OAB (ICS definition), refractory to AC, ≥8 voids/24 h ☐ Urodynamic DO or hypersensitive bladder (normal capacity, premature filling)	9	2
Brubaker et al.[9]	2008	RCT	43	Placebo 200	15-20 ID Sparing trigone	☐ Neurologically intact women, ≥21 yo ☐ Refractory ≥ 2 AC + behavioural or physical therapy ☐ ≥6 UUI and urodynamic DO	12	1
Sahai et al.[10]	2008	RCT	33	Placebo 200	20 ID Sparing trigone	☐ <80 yo, OAB symptoms ≥6 mo, Failed AC ≥6 weeks ☐ Urodynamic DO with Phasic or terminal DO		1
Sahai et al.[24]	2009	RC	65	Placebo 200	20 ID Sparing trigone	☐ ≤80 yr+ OAB symptoms + urodynamic DO + Refractory to AC ☐ Willing to perform CISC	3-4	3
Flynn et al.[11]	2009	RCT	22	Placebo 200 300	10–12 ID Along posterior wall	☐ 2 daily UUI on a 3-day bladder diary ☐ 24-h pad weight >100 g ☐ Failure of at least 1 AC and behavioral modifications	1.5	1
Cohen et al.[12]	2009	RCT	47	100 150	10–15 ID Sparing trigone	☐ *OAB-wet:* >8 voids/day and at least 1 daily episode of UUI ☐ *OAB-dry:* >8 voids/day, no UUI ☐ *Boths:* Failure to ≥2 AC for ≥2 mo	6	1
Kuo et al.[25]	2010	RC	217	100 to 200	Suburothelial or ID Include trigone	☐ Urodynamic DO with or without urinary incontinence ☐ Refractory to AC for >3 mo	6	3
Dmochowski et al.[13]	2010	RCT	313	Placebo 50–300	20 ID Sparing trigone	☐ Male and female, 18-85 yo, IOAB ≥6 mo, Failed AC ☐ ≥8 UUI episodes/week, ≤1 incontinence-free day ☐ ≥8 micturitions/day	9	1
Altaweel et al.[14]	2011	RCT	39	100–200	20 ID, include trigone	☐ Failure of symptom control despite 3 months of AC	9	1
Dowson et al.[15]	2011	RCT	21	Placebo 100	10 ID Sparing trigone	☐ OAB ☐ Failed conservative and pharmacological therapy	3	1
Rovner et al.[16]	2011	RCT	313	Placebo 100–300	20 ID Sparing trigone + dome	☐ IOAB ≥6 mo, ≥8 micturitions/day, Failed ≥1 AC ☐ ≥8 UUI episodes/week (≤1 incontinence-free day/week)	9	1
Denys et al.[17]	2012	RCT	99	Placebo 50 to 150	15 ID Sparing trigone	☐ ≥3 episodes of UUI per 3 days, ≥8 voidings/24 h ☐ Proven DO + Refractory to AC, AC ≥ 3 mo	6	1
Fowler et al.[18]	2012	RCT	313	Placebo 100 to 300	20 ID Sparing trigone + dome	☐ Male and female, 18–85 years ☐ IOAB with UUI for ≥6 mo, Refractory to AC ☐ ≥8 UUI episodes/week and ≥8 micturitions/day	9	1
Tincello et al.[19]	2012	RCT	240	Placebo 200	20 ID Sparing trigone	☐ Women with OAB and urodynamic DO ☐ Refractory to AC after 8 weeks	6	1
Nitti et al.[20]	2013	RCT	557	Placebo 100	20 ID Sparing trigone	☐ ≥3 UUI episodes in 3 days, ≥8 micturitions/day, Failed AC ☐ PVR ≤ 100 mL + Willing to perform CIC if required	3	1

(Continued)

TABLE 3. **Characteristics of the included studies**

Authors	Year	Type	Patient (n)	Dose (U)	Injection method	Inclusion criteria	Follow-up (mo)	LE
Chapple et al.[21]	2013	RCT	548	Placebo 100	20 ID Sparing trigone	☐ IOAB, Failed AC, PVR ≤ 100 mL ☐ ≥3 UUI episodes (3-day bladder diary), ≥8 micturitions/day	3	1
Liao and Kuo[26]	2013	PC	166	100	40 suburothelial Sparing trigone	☐ DO refractory to AC >3 mo	12	2
Wang et al.[27]	2014	RC	96	100	40 suburothelial	☐ Urodynamic DO with or without urinary incontinence ☐ Refractory to behavioral therapy and AC >3 mo	6	3
Osborn et al.[28]	2015	RC	160	100 200	–	☐ Persistent UUI and urinary frequency + Failed ≥1 AC ☐ Preoperative PVR reading required	ND	3
Hsiao et al.[29]	2016	PC	89	100	20 ID Sparing trigone	☐ Urodynamic DO with or without urinary incontinence ☐ Refractory to ≥ 2 AC ≥ 3 mo ☐ Persistent severe UUI (≥1 episode per day)	3	2
Owen et al.[30]	2017	RC	122	200	20 ID Sparing trigone	☐ Urodynamic DO, Refractory to AC, Incontinence not required ☐ ≥8 voids + 2 "moderate" or "severe" urge per 24h	1.5	3
Miotla et al.[31]	2017	PC	252	100	20 ID Sparing trigone	☐ Non-pregnant women >18 years ☐ OAB wet symptoms (≥8 micturitions/24h and ≥1 UUI/24h) ☐ Failed ≥2 AC ≥ 2 mo or mirabegron ≥1 month ☐ Stage ≤1 on POP-Q scale, Max flow on uroflowmetry >15 mL/s	3	2
Richter et al.[32]	2017	PC	190	200	15-20 ID Sparing trigone	☐ Non-pregnant females, ≥21 yo, OAB Refractory to ≥2 AC ☐ ≥6 UUI episodes in 3-day bladder diary ☐ Urodynamic assessment within 18 mo	6	2
Kennelly et al.[33]	2018	RC	299	100	20 ID Sparing trigone	☐ Non-neurogenic OAB, Refractory to AC ☐ Negative dipstick for nitrites and leukocytes	4-6	3
Liberman et al.[34]	2018	RC	81	100	-	☐ IOAB, Refractory to conservative and medical management ☐ First-time injection of BoNT-A	1	3
Faure Walker et al.[35]	2019	PC	65	100–300	10-20ID, sparing trigone	☐ IOAB + DO on urodynamic	1-3	2
Abrar et al.[36]	2020	PC	74	100 200	10–20 ID Sparing trigone	☐ First-time BoNT-A injections ☐ IOAB refractory to AC therapy for ≥6 weeks, Urodynamic DO	6	2
Mateu-Arrom et al.[37]	2020	RC	146	100	20 ID Sparing trigone	☐ IOAB ☐ First-time BoNT-A injection	3	3
Yokoyama et al.[22]	2020	RCT	248	Placebo 100	20 ID Sparing trigone + dome	☐ OAB ☐ ≥3 episodes of UUI + ≥8 micturitions/day in a 3-day diary	2	1
El Issaoui et al.[38]	2024	RC	397	100	10-20 ID sparing trigone	☐ IOAB	–	3
Nurkkala et al.[39]	2025	PC	94	100	20 ID, sparing trigone	☐ IOAB + Failed lifestyle modifications and ≥1 AC	3	2

Note: AC: Anticholinergic; UUI: Urge Urinary Incontinence; DO: Detrusor Overactivity; ID: Intradetrusoral; RCT: Randomized Controlled Trial; RC: Retrospective Cohort; PC: Prospective Cohort; POP-Q: Pelvic Organ Prolapse Quantification; LE: Oxford Level of Evidence.

TABLE 4. **Diversity in efficacy outcome criteria across the included studies**

Authors	Year	Patient (n)	Efficacy outcome criterion
Schmid et al.[23]	2006	100	Satisfaction estimated on a 3-point scale
Brubaker et al.[9]	2008	43	Duration of efficacy GPI
Sahai et al.[10]	2008	33	Change in MCC at 4 and 12 weeks
Sahai et al.[24]	2009	34	Change in MCC at 4 and 12 weeks
Flynn et al.[11]	2009	22	Change in daily UI episodes, UDI-6 and IIQ-7 at 3 and 6 weeks
Cohen et al.[12]	2009	47	Change in UI episodes/week at 3 mo from 3-d voiding diary
Kuo et al.[25]	2010	217	Change in perception of bladder condition at 3 month
Dmochowski et al.[13]	2010	313	Change in daily UI episodes, UDI-6 and IIQ-7 at 3 and 6 weeks
Altaweel et al.[14]	2011	39	Improvement in urodynamic values
Dowson et al.[15]	2011	21	Change in MCC
Rovner et al.[16]	2011	313	Change in MCC
Denys et al.[17]	2012	99	>50% improvement in symptoms of urgenturia and IUU
Fowler et al.[18]	2012	313	Change in MCC
Tincello et al.[19]	2012	240	Frequency of micturition/24 h
Nitti et al.[20]	2013	557	Frequency of UI/24 h and % of TBS
Chapple et al.[21]	2013	548	Frequency of UI/24 h and % of TBS
Liao and Kuo[26]	2013	166	Change in perception of bladder condition score
Wang et al.[27]	2014	96	PPBC 6-point change, UR, CISC, haematuria, PVR >150 mL and UTI
Osborn et al.[28]	2015	160	UR, UTI, subjective symptoms improvement and time length CISC
Hsiao et al.[29]	2016	100	Global Response Assessment GRA
Owen et al.[30]	2017	200	Change in ICIQ-SF, IQOL and PGI-I questionnaire
Miotla et al.[31]	2017	252	Rate of UR, duration of CISC
Richter et al.[32]	2017	190	Reduction in daily IUU or ≥50% on a bladder diary 1 week
Kennelly et al.[33]	2018	299	Rate of CISC
Liberman et al.[34]	2018	81	Rate of UR
Faure Walker et al.[35]	2019	65	Change in UDI-6 and IIQ-7 questionnaire after injection
Abrar et al.[36]	2020	74	Change in UDI-6 questionnaire
Mateu-Arrom et al.[37]	2020	146	TBS
Yokoyama et al.[22]	2020	248	Change from baseline in number of daily UI episodes at 3 mo
El Issaoui et al.[38]	2024	397	Rate of CISC
Nurkkala et al.[39]	2025	94	Change in PGI-I (good response PGI-I ≤ 4)

Note: GPI: Global Performance; Impact MCC: Maximum cystometric capacity; UI: Urinary Incontinence; IUU: Urinary Incontinence due to Urgency; UDI: Urogenital Distress Inventory; IIQ: Incontinence Impact Questionnaire; CISC: clean intermittent self-catheterisation; UTI: urinary tract infection; UR: urinary retention, UTI: urinary tract infection; TBS: Treatment Benefit Scale; PVR: post-void residual volume; PGI-I: Patient Global Imression of Improvement; PPBC: Patient's Perception of Bladder Condition.

Significant differences in uninhibited detrusor contractions are noted in 2 studies[17,23] (Table 5).

Dose-dependent efficacy

The BoNT-A dose significantly impacts efficacy. A 100-unit dose generally outperforms a 50-unit dose, while doses between 100 and 300 units show comparable efficacy at 3 months.[12,14,17,37] Brubaker's study[9] found that a 200-unit dose reduced UI by 60%, while in 2 studies, a 100-unit dose reduced UI episodes by 50%.[20,21] Doses above 150 units do not enhance efficacy but increase the risk of complications[16] (Figures 2 and 3). A 50-unit dose improves symptoms but demonstrates minimal urodynamic changes, with results similar to placebo.[13,16] However, objective results from micturition diaries or urodynamic studies do not always align with subjective patient-reported outcomes.[40]

Poor response

However, BoNT-A is not effective for everyone. 14 studies report the rate of poor responders with 25.02%

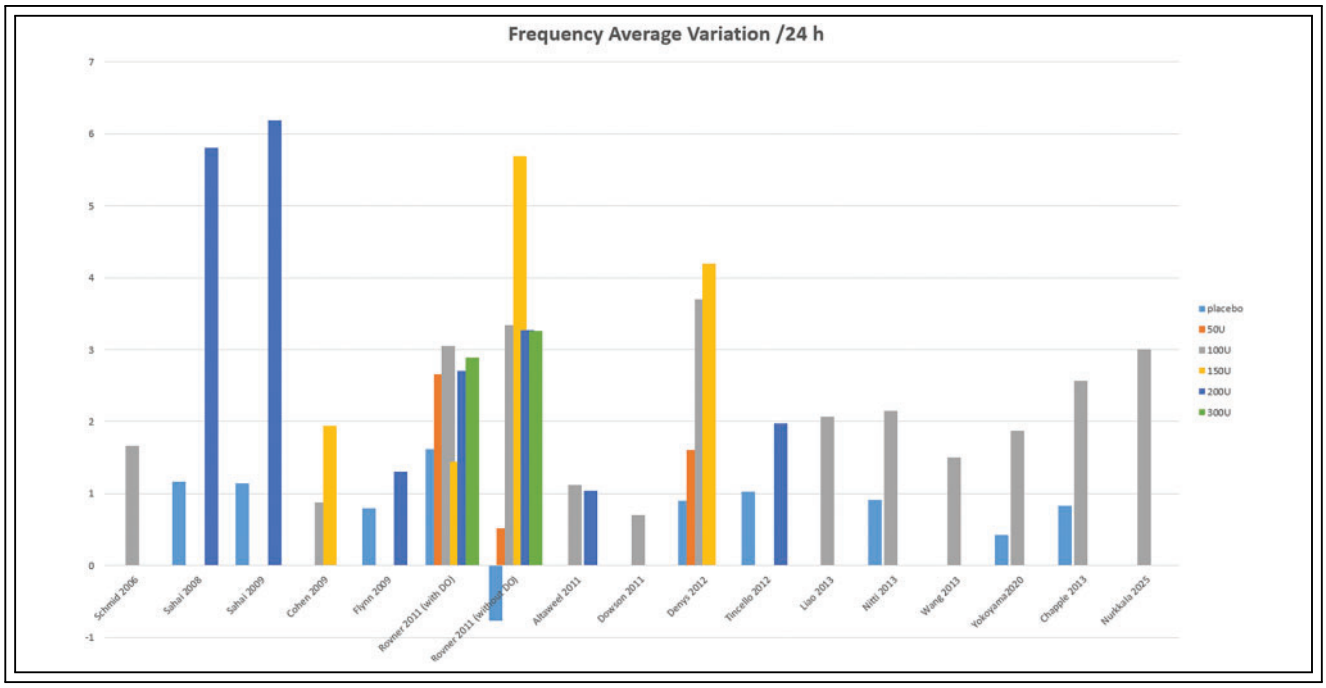

FIGURE 2. Variation of voiding frequency over a 24-h period

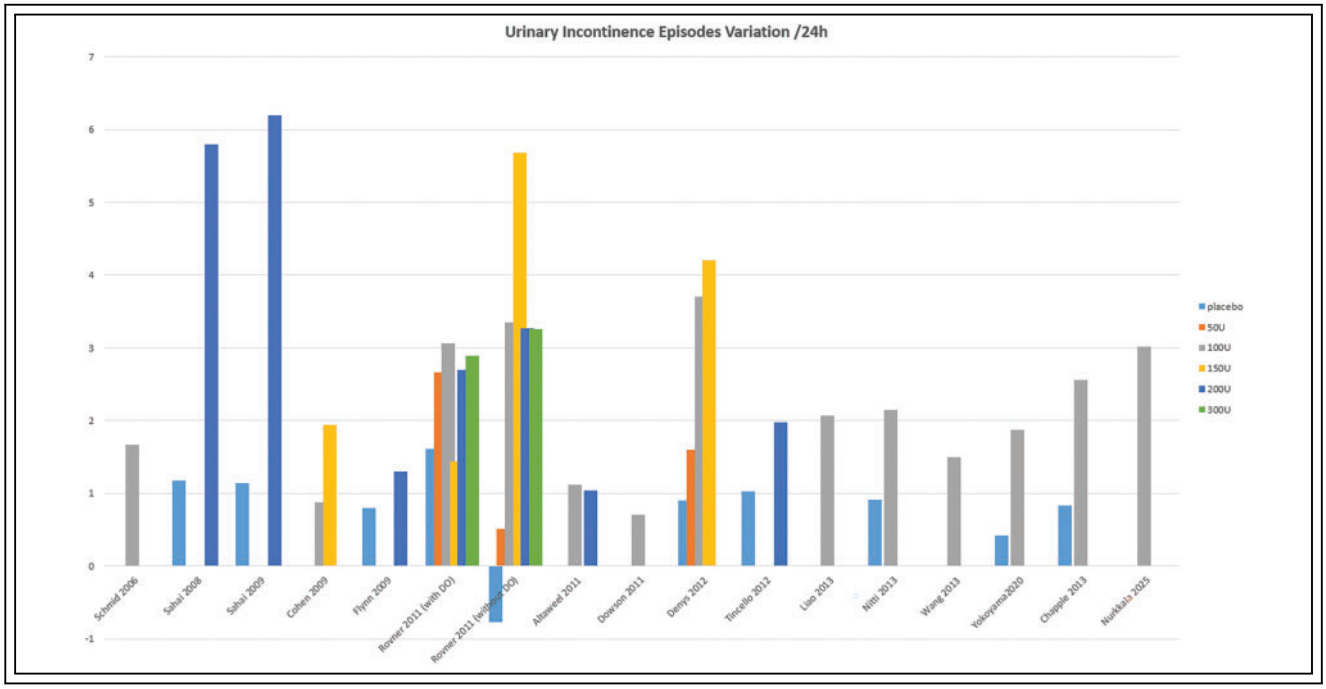

FIGURE 3. Variation in the frequency of urinary incontinence episodes over a 24-h period

in our study. There is a lack of a consistent definition of a poor response complicating direct comparisons. The most common criterion is less than 50% improvement in urgency and UI episodes. Other studies utilize scores or urodynamic criteria (Table 6). A 100-case prospective cohort[23] used a broad criterion of no urodynamic or subjective change, which could lead to the overestimation of poor responses by not

TABLE 5. **Variations in urodynamic measurements after injection**

Author	Dose	MCC (mL) before/after	Δ (mL)	VFDC (mL) before/after	Δ (mL)	P_{det} max (cmH_2O) before/after	Δ (cmH_2O)
Schmid 2006[23]	100U	246/384	+ 138 $p = 0.001$	169/222	+59 $p = 0.003$	24.5/45.1	+20.6 $p = 0.60$
	Placebo	198/168	−30 $p = 0.001$	122/92.6	−29.4 $p = 0.024$	78.67/78.67	0 $p < 0.0001$
Sahai 2008[10]	200U	181/263	+ 82 $p = 0.001$	124.3/147.1	+ 23.1 $p = 0.024$	85/44	−41 $p < 0.0001$
	Placebo	267.1/316.6	+ 49.5 $p = 0.07$	169/211.8	+ 42.8 $p = 0.09$	24.3/23.2	−1.1 $p = 0.70$
	50U	262/312	+ 50 $p = 0.09$	158/202.7	+ 44.7 $p = 0.07$	22.5/26.1	+ 3.6 $p = 0.60$
	100U	255/326	+ 71 $p = 0.002$	135.1/217.6	+ 82.5 $p = 0.06$	22.5/21.6	−0.9 $p < 0.01$
Rovner 2011[16]	150U	258/359.7	+ 101.7 $p = 0.05$	156.6/223.7	67.1 $p = 0.4$	23.8/18.5	−5.3 $p = 0.04$
	200U	280/371.5	+ 91.5 $p = 0.05$	179.5/280.3	100.8 $p = 0.05$	21.7/26.3	+ 4.6 $p = 0.6$
	300U	271.7/402.5	+ 130.8 $p < 0.01$	167.4/268.2	100.8 $p = 0.001$	23.8/22.8	−1 $p < 0.01$
	100U	290/361	+ 71 $p = 0.70$	155/343	+ 188 $p = 0.50$	29/21	−8 $p = 0.70$
Altaweel 2011[14]	200U	392/402	+ 10 $p = 0.70$	153/328	+ 175 $p = 0.35$	26/19	−7 $p = 0.53$
	Placebo	290/312	+ 22 $p = 0.009$	110/108	+ 2 $p = 0.7$		
Dowson 2011[15]	100U	259/365	+ 106 $p = 0.009$	86/149	+ 63 $p = 0.22$		
	Placebo	229/251.9	+ 22.9 $p = 0.70$	130/147.5	+ 17.5 $p = 0.60$	46.7/43.7	−3 $p = 0.60$
	50U	212/250.4	38.4 p = 0.634	110.6/176.7	+ 76.1 $p = 0.52$	29.3/35	+ 5.7 $p = 0.846$
Denys 2012[17]	100U	249/334.5	85.5 $p = 0.112$	158.4/234.1	+ 75.7 $p = 0.47$	49.3/35.5	−13.8 $p = 0.16$
	150U	220/311.3	91.3 p = 0.043	118.8/228.8	+ 110 $p = 0.05$	42.4/31.7	−10.7 $p = 0.004$
Wang 2014[27]	100	289/354	+ 65			22.7/19.6	−3.1
Liao 2013[26]	100	254/342	+ 88			23.9/20.4	−3.5
Mateu-A 2020[37]	100	216/255	+ 39 $p = 0.006$	87/146	+ 59 $p = 0.002$	57/52	−5 $p = 0.001$

Note. MCC: Maximum cystometric capacity; VFDC: Volume at the first detrusor contraction; P_{det} max: Maximum detrusor pressure; Δ: Average variation.

accounting for subtle improvements. One RCT[11,14] focused on no MCC change, though this approach may neglect other important outcomes like quality of life. Several studies[18,25,26] used patient-reported outcomes like a significant decrease in PPBC, which is subject to patient bias. Liao et al.[25] required a PPBC decrease at 12 months. This long-term assessment might miss earlier markers of failure, influenced by individual perceptions of bladder function. Symptom-based definitions,[14,29,31] like <20%

TABLE 6. **Summary of studies on poor response and adverse outcomes**

Author	Definition of poor response	Poor responders (%)	Large PVR (%)	CISC (%)	UTI (%)
Schmid et al., 2006[23]	No urodynamic and subjective change	8		15	12
Sahai et al., 2008[10]	No pertinent MCC change	15.2	35	29	28
Cohen et al., 2009[12]	<50% frequency reduction	37			
Flynn et al., 2009[11]			26.6	6.5	13
Dmochowski et al., 2010[13]			20	14.9	39
Dowson et al., 2011[15]	Significant PPBC decrease	14.3	18	14.3	36.4
Altaweel et al., 2011[14]				7.7	5.1
Rovner et al., 2011[16]			**17.67**	10	14.8
Denys et al., 2012[17]			15	11.8	6.7
Tincello et al., 2012[19]			19	16	31
Chapple et al., 2013[21]			3.3	5.8	24.1
Nitti et al., 2013[20]			11.2	5.8	24.5
Kuo et al., 2013[25]			47.5	8.3	14.3
Liao et al., 2013[25]	PPBC decreases <2 or stays the same at 12 mo	Frail 65 yo: 33.2 <65 yo: 16.9	16.4	7.2	15.7
Wang et al., 2014[27]	PPBC at 6-month	Diabetic: 44 Non-diabetic: 39	Diabetic: 60 Non-diabetic: 33	Diabetic: 10.4 Non-diabetic: 6	12.5 both group
Osborn et al., 2014[28]				35	16
Hsiao et al., 2016[29]	Global response assessment <2 at 3 months	36.3			
	≤20% urgency frequency upgrade at 6-wk	23.8			
Owen et al., 2016[30]	≤20% leakage frequency upgrade	15.6		23.2	18.9
	≤10% voiding frequency upgrade	19.7			
Richter et al., 2017[32]	No UUIE reduction+ <50% reduction in all diaries	12.7			
Liberman et al., 2017[34]	<50% improvement on global response assessment	25	25.2	20.4	20.4
Miotla et al., 2017[31]			6,2	6,2	
Kennelly et al., 2018[33]			3.5	2.7	26.3

(Continued)

TABLE 6. **Summary of studies on poor response and adverse outcomes**

Author	Definition of poor response	Poor responders (%)	Large PVR (%)	CISC (%)	UTI (%)
Abrar et al., 2020[36]	<16.7 UDI-6 questionnaire decrease at 1 mo	31.9		43.8	34.2
Mateu-Arrom et al., 2020[37]	TBS score of 3 or 4	37.7		23.8	16.9
Yokoyama et al., 2020[22]			6	6	13
Nurkkala et al., 2025[39]			8.8	6.64	9.96

Note: PPBC: Patient Perception of Bladder Condition; TBS: Treatment Benefit Scale; UUIE: Urgency Urinary Incontinence Episodes.

improvement in urgency[29] or <50% reduction in urgency frequency,[14] yet may be influenced by recall bias or fluctuating symptoms, not fully reflecting the complexity of treatment responses. Similarly, a recent RCT[33] and a prospective study of 74 cases[35] focused on symptom improvement thresholds using subjective measures (e.g., UDI-6), which may not reflect underlying physiological changes. Finally, Mateu-A et al.[36] used the TBS score, a more structured approach, though it may obscure individual patient experiences.

Adverse effects

Post-void residual

23 studies have investigated the occurrence of AE. Generally, BoNT-A is well tolerated and safe in routine practice, with less than 5% of severe complications.[23] High PVR is the most commonly reported AE, documented in 17 studies with an overall rate of 22.4% in our work, and exceeding 25% in 6 studies.[10,11,24,25,29] This variation can be attributed to differing definitions of significant PVR (≥150 mL, ≥200 mL, or greater). PVR typically occurs within the first month post-injection[20,26] and is dose-dependent, with a notable increase observed at doses starting from 150 units of toxin.[16] At a dose of 100 U, less than 10% of studies report PVR,[20,21,22,28,35] whereas at 200 U, over 20% report PVR (Table 6).

Clean intermittent self-catheterization

The rates of CISC across the 23 studies vary widely, from 6.2%[30] to 43.8%,[35] with an average of 14.02% in our study. This variability can be explained by differences in the criteria used to define the need for CISC, which are generally based on clinical signs and/or PVR. No standardized protocol currently exists for determining when to initiate CISC.[30] The need for CISC decreases with the toxin dose: rates exceed 40% at 300 units, around 30% at 200 units, less than 11% at 100 units, and only 3% at 50 units.[16,24] When required, CISC typically lasts six weeks or less[20] (Table 6).

Urinary tract infections

The frequency of UTIs shows also considerable variation, as studies employ different definitions. Among the 23 studies, the average UTI rate is 19.4%, with a range from 5.1%[17] to 36.4%.[18] The occurrence of UTI may exacerbate PVR, with a risk ranging from 10% to 30%, depending on the PVR threshold.[14,16,17] Managing UTI is essential due to potential complications. In a series of 299 cases, the presence or absence of UTI was the primary safety criterion[32] (Table 6).

Other adverse events

Local AE following BoNT-A injections include macroscopic hematuria, with reported occurrences ranging from 0.2%[15] to 23.1%,[17] with an intermediate occurrence of 3.6%.[24] Dysuria is reported less frequently,[23,24] moderately (10%,[37]) or more frequently (46.5%.[34]) Pain at the injection site and non-bacterial cystitis are also noted.[37]

Rare systemic AE due to toxin diffusion include respiratory depression,[41] muscle weakness,[42] fatigue (2%),[43] skin rash,[44] nasopharyngitis,[37] and gastroparesis.[16] Rare cases of urinary retention,[16] pyelonephritis,[44] and bilateral hydronephrosis[24,44] have been documented. Importantly, no cases of mortality have been reported in multiple studies.[43–48]

Predictive factors of poor response

10 studies have identified factors associated with a poor response to BoNT-A injections (Table 7).

Non-modifiable factors

Male gender is a predictive factor for a poor response, as reported in the studies by Hsiao (OR = 3.75, 95% CI 1.40–10.06, $p = 0.009$)[29] and Abrar (OR = 5.45, 95% CI 1.83–16.47, $p = 0.002$).[36] Up to 36% of males show an inadequate response to BoNT-A injections,[29] possibly due to voiding dysfunction linked to benign prostatic hyperplasia.[41] Although the efficacy of BoNT-A has been widely studied in women, there is less research on its use in men. Improvement in quality-of-life scores is statistically more significant in women.[42] Table 7 summarizes predicting factors of poor response. Age is another factor associated with poor response, identified in 4 studies.[12,26,30,32] Cohen et al.[12] define the threshold at 55 years ($p = 0.03$)[12] but only in univariate analysis, while Liao et al.[26] set it at 65 years in the "Frailty" subgroup defined by specific criteria (see Table 7). Advanced age is particularly predictive of poor continence response.[12]

TABLE 7. **Predicting factors of poor response and adverse events**

Study	Factors predicting poor response	Factors predicting UR and CISC	Factors predicting UTI
Schmid et al., 2006[23]	<10 mL/cmH_2O DC-<100 mL MCC-Bladder wall fibrosis on biopsies		
Sahai et al., 2008[10]	P_{det} max >110 (Sen 0.86; Spe 1.0)	Mean Qmax< 15 ($p = 0.003$)	
Cohen et al., 2009[12]	Age 55≤ ($p = 0.03$)		
Kuo et al., 2013[25]		Male (OR = 9.2, 95% CI 1.5–34.0, $p = 0.013$)-Baseline PVR >100 mL (OR = 9.9, 95% CI 7.2–44.7, $p = 0.003$)	Female ($p = 0.002$) Male with retained prostate ($p = 0.024$)
Liao et al., 2013[25]	Frail elder at 12mo ($p = 0.041$)	Large PVR in frail elder ($p = 0.018$)	
Wang et al., 2014[27]	No difference between diabetic and non-diabetic groups	UR: no difference diabetic and non-diabetic groups ($p = 0.357$) Large PVR: presence of diabetes ($p = 0.007$)	No difference between diabetic and non-diabetic groups ($p = 0.621$)
Osborn et al., 2015[28]		Preoperative PVR (OR = 1.27, $p < 0.01$) + large DC (OR = 1.05, $p = 0.05$)	
Hsiao et al., 2016[29]	Male gender (OR = 3.75, 95% CI 1.40–10.06, $p = 0.009$)	3 mo VE <87 (OR = 0.973, $p = 0.03$)	
Owen et al., 2016[30]	For change in urgency episodes ≤20%: Smoking (OR = 2.89, 95% CI 1.08–7.73, $p = 0.034$) For PGI: age (OR = 1.04, 95% CI 1.0–1.09, $p = 0.063$) -BMI (OR = 1.07, 95% CI 1.0–1.16, $p = 0.065$) For incontinent at follow-up: baseline leakage episodes (OR = 1.17, 95% CI 1.04–1.31, $p = 0.007$)		

(Continued)

TABLE 7. **Predicting factors of poor response and adverse events**

Study	Factors predicting poor response	Factors predicting UR and CISC	Factors predicting UTI
Richter et al., 2017[32]	0.50 HUIM3 (per 0.30 points increase on HUI-3; 95% CI 0.23–0.77, $p < 0.001$) -age ($p = 0.001$) -↑ FCI (OR = 0.84, 95% CI 0.71–0.99, $p = 0.041$)		
Miotla et al., 2017[31]		≥3 vaginal deliveries (OR = 6.86, $p < 0.01$) -≥68 yo ($p < 0.01$)	
Abrar et al., 2020[36]	Male gender (OR = 5.45, 95% CI 1.83–16.47, $p = 0.002$)	Male (OR = 5.14, 95% CI 1.41–18.72, $p = 0.013$) -Hysterectomy (OR = 4.55, 95% CI $p = 0.038$) -Qmax <15 (OR = 0.91, 95% CI 0.83–0.99, $p = 0.023$) | 25 (34.2%)	Lower female PIP1 (OR = 0.93, 95% CI 0.87–1.00, $p = 0.05$) -CISC (OR = 5.26, 95% CI 1.38–20.00, $p = 0.015$)
Mateu-Arrom et al., 2020[37]	Higher BOOI		
El issaoui et al., 2024[38]		MUI (OR = 0.23, 95% CI 0.07–0.79) -MUS (OR = 1.96, 95% CI 0.81–4.71) -Anterior colporrhaphy (OR = 3.71, 95% CI 1.52–9.06) -MCC/10 mL increment (OR = 1.03, 95% CI 1–1.06)	

Note: Sen: sensitivity; Spé: specificity; P_{det} max: maximum detrusor pressure; OAB: overactive bladder; MUI: mixed urinary incontinence; UUI: Urgency urinary incontinence; MUS: midurethral sling; MCC: maximal cystometric capacity; OR: Odds ratio; CI: Confidence interval; BOOI: bladder outlet obstruction index; HUIM3: Health Utilities Index Mark 3; FCI: functional comorbidity index; DC: detrusor compliance; VE: voiding efficiency; PIP1: projected isovolumetric pressure value;UR: urinary retention. Frail elder: three of: unintentional weight loss, dyspnea, weakness, reduced physical activity.

Modifiable factors

A high body mass index (BMI) has been linked to a less favorable treatment response, particularly for the PGI score, although the precise BMI threshold for this effect remains debated.[30] Smoking is another factor for poor response, found in one study (OR = 2.89, 95% CI 1.08–7.73, $p = 0.034$) regarding a reduction in urgency episodes (≤20%).[30] The presence of diabetes is not a factor for poor response in a study specifically comparing this criterion.[27]

Urodynamic factors

Urodynamic parameters prior to injection may also predict a poor response, as indicated in 3 studies. Significant factors include elevated Pdet max (>110 cmH_2O),[24] high bladder outlet obstruction index (BOOI),[36] low detrusor compliance (<10 mL/cmH_2O),[30] and reduced MCC (<100 mL).[30] Schmid additionally highlighted bladder wall fibrosis, observed on vesical biopsies, as a contributing factor to a poor response.[23]

Others factors

Post-injection complications have been correlated with a poor response, such as CISC,[35] UTI, and hematuria, potentially due to bladder inflammation and exacerbation of urinary symptoms.[25] Richter et al.[32] proposed using indices correlated with poor response, such as the Health Utilities Index Mark 3 (HUI-3) (per 0.30-point increase; 95% CI 0.23–0.77, $p < 0.001$) and the Functional Comorbidity Index (FCI) (OR = 0.84, 95% CI 0.71–0.99).

Predictive factors for adverse events

Post-void residual and clean intermittent self-catheterization

Predictors for the necessity of CISC have been reported in 9 studies, (Table 7). 2 studies identified age as a negative predictive factor, with a threshold starting at 68 years[31] or specifically in the subgroup of "≥65 years fragile elderly".[26] Male gender is a second predictive factor in 2 studies (Kuo et al.[25] OR = 9.2, 95% CI 1.5–34.0, $p = 0.013$; Abrar et al.[36]: OR = 5.14, 95% CI 1.41–18.72, $p = 0.013$), potentially due to the association between age and benign prostatic hyperplasia. Certain gynecological histories appear to be predictive of the risk of CISC. A history of hysterectomy increases the risk by 4.5 times (95% CI 1.09–18.8, $p = 0.038$),[36] likely related to denervation of the bladder wall or bladder neck, resulting in reduced sensation during filling and increased bladder capacity.[43] A history of ≥3 vaginal deliveries (OR = 6.86, $p < 0.01$)[31] and anterior colporrhaphy (OR = 3.71, 95% CI 1.52–9.06)[38] are also associated with increased risk. Additionally, comorbidities such as diabetes mellitus[27] and congestive heart failure[6] are linked to higher PVR values after toxin injection. Diabetes mellitus lead to cystopathy, detrusor underactivity and elevated PVR.[27] However, aside from PVR >150 mL, diabetes does not significantly affect symptoms or urodynamic parameters after three months.[27,37] Finally, the presence of mixed UI and a history of mid-urethral sling procedures appears to be a risk factor for urinary retention.[38] Several urodynamic factors are statistically linked to the need for CISC, including a PVR ≥ 100 mL,[25,28] large bladder capacity,[28] reduced maximum urinary flow rate,[24] and in women a low projected isovolumetric pressure (PIP1) ≤50.[24] In men, factors such as a low bladder contraction index (BCI) ≤ 120 and a high bladder outlet obstruction index (BOOI) are associated with the need for CISC.[24]

Urinary tract infections

3 studies[25,27,40] examined factors related to UTI. Women ($p = 0.002$) have a threefold higher susceptibility to post-injection UTI,[25] as do men with benign prostatic hyperplasia. Post-injection CISC increases the risk by a factor of five[36] (95% CI: 1.38–20.00, $p = 0.015$). For women, a low pre-injection (PIP1) serves as a predictive factor for UTI.[36] In men, a decrease in the bladder contraction index (BCI) is not correlated with an increased risk of UTI.[25] Furthermore, the presence of a substantial PVR (PVR) has been associated with an increased likelihood of UTI, although the exact threshold varies between studies.[9,25] Interestingly, diabetes mellitus does not appear to elevate the risk of infections post-injection.[27]

Table 7 summarizes predicting factors of adverse events.

Discussion

We observed variability in BoNT-A efficacy measures. Twenty-five studies used different scores for symptom improvement, while six studies relied on urodynamic parameters (Table 4). The lack of standardized definitions complicates assessment and has been widely discussed in the literature. A meta-analysis including 38 RCTs reported 62 different BoNT-A outcome measures.[7] In another systematic review of 19,994 participants, 15 different QoL scores were identified, with OAB-q, PPBC, I-QOL, and IIQ-7 being the most common.[49] We propose defining efficacy as a >50% improvement in urinary urgency and urge urinary incontinence (if present), as assessed by a bladder diary, or a >10-point change in I-QOL. We prefer clinical criteria over urodynamic parameters due to the invasive, poorly tolerated nature of urodynamics and their impracticality for long-term monitoring, given BoNT-A's temporary effects. We chose urgency and urinary incontinence as key symptoms of OAB, as they most significantly impact patients' QoL.[8] We selected I-QOL due to its demonstrated strong reliability, validity, and responsiveness in QoL assessment, as shown in a meta-analysis of 19,994 cases.[49] The 10-point change in I-QOL is an extrapolation based on an RCT by Yalcin et al.,[50] who identified thresholds for the minimal clinically important difference in I-QOL. In their systematic review, Abrar et al.[6] recommend using the concept of the "minimally important difference",[51] which represents the smallest significant change in QoL, combined with a voiding diary as an objective benchmark (51). The CHORUS Groups, an international collaboration for harmonizing outcomes in urogynaecology, are developing unified Core Outcome Sets (COS) and Core Outcome Measure Sets (COMS) for future research.[52]

In our study, the efficacy of BoNT-A in OAB is well-documented, with the strongest evidence. Ten RCTs (Level 1) report a reduction in voiding frequency compared to placebo (Figure 2), and eleven RCTs a UI episodes drop (Figure 3). High-quality RCTs[10,16,23] also consistently report nocturia improvement. These conclusions are consistent with the existing literature. BoNT-A reduces micturition frequency (−0.7 to −2.8/day) and urgency episodes

(30%–69%), similar to anticholinergics.[53] However, it has a stronger impact on UI episodes, with reductions of 55%–79%.[46] At 3 months, it doubles the continence rate (23% vs. 11%, $p < 0.003$),[54] significantly improving quality of life. BoNT-A is especially effective in patients intolerant to anticholinergics.[46]

BoNT-A's efficacy and AE are dose-dependent. Doses above 150 U do not provide additional benefits but increase adverse effects. In our study, a 313-case study comparing 50 to 300 U showed no significant improvement with higher doses, but increased adverse effects.[16] Similarly, two RCTs (100 vs. 150 U)[14] and (100 vs. 200 U)[17] found no significant difference. in UUI reduction (67% vs. 75%)[14] or complete dryness ($p = 0.10$),[14] QoL ($p = 0.001$)[17] with significant differences in PVR ($p = 0.002$).[14] Additionally, a 99-case RCT (100 U vs. 150 U) showed that 100 U had reasonable efficacy and a lower risk of high PVR ($p = 0.0003$).[20] These results are consistent with a recent pilot study studying predicting elevated postvoid residual urine volume.[55]

Repetitive BoNT-A injections consistently lead to positive clinical outcomes and sustained quality of life, supported by strong evidence.[44] The benefits of reinjections are similar to those of the initial treatment,[23] and repeated injections do not negatively affect bladder wall integrity,[56] despite the need for CISC. Anxiety and depression scores improve after the second injection and remain stable.[57] Over the years, with an average of six injections, 74% to 83% of patients report high satisfaction due to reduced incontinence episodes.[23]

BoNT-A injections are generally well tolerated.[34] In our study, we found an AE rate of 21.7%, consistent with the literature. A 2019 European report on idiopathic OAB indicates an AE rate of 26% after the first injection and 22% after the second.[56] A time-based analysis of post-injection adverse effects showed that PVR peaks at week 2, increasing, then declining by week 36.[14] In 3 RCTs, CISC was most common within the first month.[16,19,20] UTIs generally occur in the first 2 weeks, concomitant with the increase in PVR,[11,18] related to urinary stasis.[15] No specific time-based data on adverse effects from repeated injections were found in long-term series.[58–61]

These main AEs are typically mild to moderate, transient, and manageable with standard antibiotics and clean intermittent CISC.[44,45] Despite this, these AEs have a significant impact on treatment adherence. A 5-year follow-up study[48] revealed that, aside from cases of total or partial ineffectiveness (37%), reasons for discontinuing treatment included the need for CISC (11%) and UTI (9%), leading to a 25% long-term treatment discontinuation rate among patients. Overall, the rate of treatment discontinuation varies across long-term studies: 18.9% at 5 years in a French multi-center study,[58] 25% at 6 years in a real-life study,[61] and up to 38.9% at 4 years in a 90-case retrospective analysis.[59]

In our review, we identified several predictive factors for AE following BoNT-A injections (Table 7). The strength of these associations varies by study design, sample size, and statistical methods. Only one Level 1 RCT[11] according to the Oxford Levels of Evidence scale investigated predictive factors for AE, finding that pre-injection Qmax <15 predicts CISC ($p = 0.003$), supported by a prospective large cohort[35] with an OR of 0.91, though selection bias limits causality.

Male gender is a consistent predictor of CISC in two large cohorts: one retrospective Level 3 with 217 cases[25] and one prospective Level 2 with 146 cases,[35] with ORs ranging from 5.14 ($p = 0.013$) to 9.2 ($p = 0.13$), likely due to concomitant bladder outlet obstruction. Prospective cohort studies offer stronger causal evidence compared to retrospective studies, which are prone to biases.[62] These data are supported by a recent meta-analysis, which, however, highlighted low evidence and limited information regarding the safety of BoNT-A for male OAB.

Preoperative PVR is also widely reported as a factor for CISC, with confirmation from 3 large retrospective cohorts[15,25,26] and one prospective controlled study.[35] However, its significance diminishes when associated with frailty ($p = 0.18$) or diabetes ($p = 0.07$), indicating moderate uncertainty.

The role of age as a predictor for CISC is unclear. Only one Level 2 prospective cohort[30] found it significant in 252 cases, with potential selection bias. However, a meta-analysis focusing specifically on the elderly population shows an increased risk of CISC over 65 years old (RD: 0.154; 95% CI: 0.058 to 0.251).[63]

Gynecological historywas identified as a predictor in two large Level 2 (n = 146)[35] and Level 3 (n = 397)[38] cohorts, with high ORs (4.55 for hysterectomy2,[35] 3.71 for anterior colporrhaphy).[38] However, wide confidence intervals (1.09–18.8 for hysterectomy2,[35] 1.52–9.06 for colporrhaphy[38]) reduce precision, necessitating further prospective studies. We did not find other studies in the literature reporting these conclusion.

We found in a 122 case Level 3 study that high BMI prédit une poor answer (OR = 1.07, 95% CI 1.0–1.16,

$p = 0.065$).[29] This contrasts with the results of a retrospective study from the literature involving 185 cases, which specifically studied injections in individuals with high BMI.[64]

Urodynamic parameters, such as lower female PIP1 and MCC/10 mL increments, are strongly associated with AEs. Studies with satisfactory quality (Levels 2[35] and 3[38]) report consistent ORs with narrow confidence intervals, supporting their predictive value. These results are also found in a large meta-analysis.[6]

We identified age as a predictor of poor response in one RCT[14] and a level 2 prospective cohort.[25] In contrast, literature data from a pooled analysis of Moore's trial[65] showed no statistically significant differences in efficacy between patients over and under 65 years of age. A 2024 meta-analysis including only elderly patients highlights the need to weigh the benefits of BoNT-A for UI against its risks in this population, particularly due to their increased risk of infections and urinary retention.[63]

Tincello et al.[19] found that DO does not impact BoNT-A efficacy, suggesting that urodynamic confirmation may not be necessary. In a study by Mateu-Arrom et al.,[36] a higher BOOI predicted poor response in men, not due to bladder contractility but rather to urethral resistance, which appears to be a more important factor in treatment outcomes. This suggests that urodynamic testing may still be required for patient selection. Level 2[12] and level 3[35] included studies that suggested that reduced detrusor contractility may predict the need for CISC. However, three studies found no link between CISC rates and the Bladder Contractility Index.[10,16,33]

The pre-injection PVR remains a subject of debate. While high-level evidence includes studies that found no association between pre-injection PVR and CISC,[12,19,25] many other robust evidence consider a high pre-injection PVR as an exclusion criterion in their study design.[23,24,27] This discrepancy is explained by a dual semantic issue widely discussed in the literature, as highlighted by two large meta-analyses[66,67] linking outcome variability to differences in initiation criteria for CISC across studies and the definition of what constitutes a high PVR.

Liao et al.[26] found that diabetes increases PVR (60.4% vs. 33.3%; $p = 0.007$), likely due to cytopathic and detrusor underactivity. These data contradict those from the literature, including a retrospective cohort of 565 patients,[68] in which diabetic patients had a similar rate of high PVR and urinary retention requiring CISC as non-diabetic patients.

We found that statistically significant risk factors for UTI include female gender[25] and a CISC,[35] consistent with findings by Everaert et al.[69] Further studies are needed to explore methods for preventing post-injection UTI.[45]

The relationship between AEs and poor treatment response remains unclear, possibly due to exacerbation of bladder inflammation and worsening of lower urinary tract symptoms.[70] Future perspectives are being explored for cases of poor response to BoNT-A. Integrating BoNT-A with rehabilitative strategies has shown promising results in spastic diplegia, reducing spasticity and improving gait.[71] This combined approach could also benefit OAB by pairing BoNT-A with behavioral or physical therapies to enhance bladder control. However, further studies are needed.

This review has several limitations that should be considered. Most studies included providing level 3 evidence, with many being retrospective cohorts, which inherently carry a risk of bias, particularly about selection and recall biases. Variations in Botulinum Toxin-A doses across studies, coupled with the lack of standardized definitions for poor response and CISC initiation, further complicate direct comparisons. Additionally, many studies suffer from small sample sizes, and some may involve overlapping populations, which could lead to potential confounding. Importantly, while the moderate quality of studies is acknowledged, the potential impact of publication bias, often observed in studies with positive results, has not been thoroughly discussed. The absence of long-term data further limits the generalizability of findings. Another key limitation is the lack of data on covariates such as comorbidities and concomitant medications. Only two studies addressed comorbidities: one found no link between diabetes and treatment response or infection risk,[26] and another linked frailty in older adults to poor response, without details on polypharmacy.[25] The remaining studies did not report these factors, limiting the assessment of their role in adverse events and treatment outcomes. Future studies should account for these covariates. Despite these limitations, consistent trends, particularly in short-term efficacy and safety, were observed across the studies.

Conclusion

In summary, this comprehensive review highlights the efficacy of intradetrusorial BoNT-A injections for refractory idiopathic detrusor overactivity. Results

consistently demonstrate significant symptom improvement, enhanced quality of life, and urodynamic benefits. Factors like age, gender, and the potential need for CISC influence treatment response. Despite challenges, successive injections maintain positive outcomes and manage AE, affirming BoNT-A as a viable, sustainable therapeutic option. This knowledge guides clinical decisions, with room for further research to refine this promising approach.

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Author Contributions

The authors confirm contribution to the paper as follows: Study conception and design: Salim Lachkar, Ahmed Ibrahimi; Data collection: Salim Lachkar, Ahmed Ibrahimi, Imad Boualaoui; Analysis and interpretation of results: Salim Lachkar, Ahmed Ibrahimi; Draft manuscript preparation: Salim Lachkar, Hachem El Sayegh, Yassine Nouini; Final manuscript review and approval. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, Salim Lachkar, upon reasonable request.

Ethics Approval

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest to report regarding the present study.

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